REMARKS

Favorable consideration and allowance are respectfully requested for claims 1-52 in view of the foregoing amendments and the following remarks.

Certified translations of German priority application no. 101 37 488.7 and of International Patent Application No. PCT/EP02/08729 are submitted herewith.

35 U.S.C. § 112

The rejection of claims 47 and 50 – 52 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement, is respectfully traversed.

The enablement requirement is satisfied where the specification describes the claimed subject matter in such a way as to enable any person skilled in the art to which it pertains to make and/or use the invention. Thus, enablement is judged in view of the combined teachings of the specification and the knowledge of one skilled in the art.

The Office Action asserts that the term "alleviating" means "completely curing, see page 2 of the Office Action. This is incorrect as alleviating simply means to lessen. The Merriam-Webster Online Dictionary provides two definitions for alleviate:

a: to make (as suffering) more bearable <her sympathy alleviated his distress>

b: to partially remove or correct.

Webster's Revised Unabridged Dictionary (1913) provides three definitions for alleviate:

1. To lighten or lessen the force or weight of.

2. To lighten or lessen (physical or mental troubles); to mitigate, or make easier to be endured; as, to alleviate sorrow, pain, care, etc.

3. To extenuate; to palliate.

Webster's New World Dictionary defines alleviate as:

1. To make less hard to bear; lighten or relieve.

2. To reduce or decrease.

Copies of these definitions are attached hereto as Appendix A. None of these definitions indicates that "alleviating" means completely curing. To the contrary, the definitions provided in these dictionaries consistently indicate that alleviate means only to lessen.

The Office Action admits that the specification is enabling for treating pain, see page 2 of the Office Action. If the specification adequately enables treating a condition, it necessarily also provides for alleviating a condition. One cannot successfully treat a condition without at least partially alleviating the condition. Because claim 47 should be properly read to cover lessening pain, the claim is properly enabled. To the extent the rejection is based on an understanding that the claims were directed to completely curing, the rejection is improper and should be withdrawn.

The rejection also appears based, in part, on the claim recitation of treating or inhibiting certain conditions listed in claims 50-52. The Office Action points out that the specification teaches the inhibitory effect of the compounds on the formaldehyde-induced nociception in rats as well as binding affinity for the glycine-binding site of the NMDA receptor, see page 3 of the Office Action.

The specification makes clear that the claimed compounds are active as NMDA-antagonists. Paragraph [0009] indicates that one object of the invention

involves providing NMDA antagonists. Paragraph [0011] indicates that the compounds are NMDA antagonists. Further, one of skill in the art would appreciate that the receptor binding assay provided for in example 50 on pages 55-57 is such that only NMDA-antagonists show affinity to the glycine binding site. Consequently, a compound shown to have an affinity to the glycine binding site of the NMDA-receptor is an NMDA-receptor antagonist.

The therapeutic utility of NMDA-antagonists for treating the diseases provided in claims 55 and 56 of the specification was well known at the time of filing the present application, as evidenced by the literature cited in paragraph [0007] of the specification. As further evidence of the knowledge that the glycine binding site of the NMDA-receptor channel is a suitable target for treating the various disorders claimed in claims 55 and 56, 13 pages from the drug abstract listings in the Drug Data Report published by Prous Science of Barcelona, Spain are provided in Appendix B hereto.

For example, compound 225249 is described as an antagonist at the glycine site of the NMDA receptor. The abstracts indicates that the compound is useful for the treatment and prophylaxis of cerebral ischemic/anoxic disorders, and for the treatment of neurodegenerative disorders such as Parkinsonism and Alzheimer's disease, as well as epilepsy, schizophrenia and migraine. Thus, compound 225249 is described as having the capability to treat a wide variety of conditions based on its affinity for the NMDA receptor.

In another example, compound 315794 is described as a glutamate antagonist with activity against sites that include the glycine binding site of NMDA receptors. Said compound is described as being useful for the treatment of cerebral ischemia, chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and Huntington's disease, seizure disorders, schizophrenia, anxiety, pain and drug abuse.

The compound 198235 which acts as an NMDA receptor antagonist is a useful agent for the treatment of neurotoxic injury associated with anoxia or ischemia following stroke, cardiac arrest and perinatal asphyxia.

Compounds 266182 and 269005 are both described to be antagonists acting at the glycine binding site of NMDA receptor channels and can be used in the treatment of stroke, cerebral hypoxia/ischemia, Alzheimer's disease, Parkinson's disease and Huntington's disease. In addition compound 269005 can also be used as an anticonvulsant, analgesic, antidepressant, anxiolytic and antipsychotic agent.

The compound 257448 which is a NMDA receptor antagonist that binds to the glycine binding site associated with the NMDA receptor channel is useful for the treatment or prevention of neurodegenerative disorders such as stroke, cerebral ischemia, epilepsy, Alzheimer's disease, Parkinson's disease and Huntington's Chorea and anoxia. Another type of compound useful in such CNS disorders is compound 240624.

Other literature citations, which disclose the relationship between the given indications and the glycine binding site of the NMDA receptor channel include:

M.P. Heyes et al., J. Neurochem. 55, 338-341, 1991 (AIDS-dementia); S. Pirot et al., Eur. J. Pharmacol. 285 (1), 45, 1995 (Anaesthesia);

R.Y. Bergeron et al., J. Med. Chem. 39 (19), 2461-2471, 1996 (Diarrhea);

A. Paul et al., J. Pharmacol. Exp. Ther. 302, 50-57, 2002 (Encephalomyelitis);

N.N. Osborne et al., Surv. Ophthamol. 43, Suppl. 1, 102, 1999 (Glaucoma);

X.M. Yu et al., Pain 68 (1), 169-178, 1996 (Inflammation);

G.J. Spencer et al, BMC Cell Biology 4, 9, 2003 (Osteoporosis);

M. Duan et al., Proceedings of the National Academy of Sciences USA 97 (13), 7597, 2000 (Ototoxicity);

K. Tan-No et al., Pain 86(1-2), 55, 2000 (Pruritus);

M.J. Guitton et al., J. Neuroscience 23, 3944-3952, 2003 (Tinnitus);

P.J. Ambroso et al., J. Am. Acad. Child Adolesc. Psychiatry 40, 1115, 2001 (Tourette's syndrom); and

W.C. de Groat, European Urology 34, Suppl. 1, 2, 1998 (Urinary Incontinence).

As evidenced by the literature, the relevance of NMDA-antagonsists to a wide variety of conditions or disease states is known to persons of skill in the art. Consequently, one of skill in the art would expect that the presently claimed compounds, which are active as NMDA-antagonsists, would exert a beneficial effect in the treatment of these diseases. Suitable delivery forms for administration are described in the specification, as are suitable amounts of the compound to be administered, see pages 31-33. Accordingly, the claims are properly enabled.

The U.S. Court of Customs and Patent Appeals has stated that "[t]The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367 , 369 (CCPA 1971). The court also added that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 169 USPQ 367 , 370 (CCPA 1971). The present record includes no

such statement or other explanation as to why the truth of the accuracy of statements in the disclosure should be doubted.

Further, all of the compounds contemplated by claims 50-52 share a common structure of corresponding to formula I. There is nothing in the present record to suggest any reason why these compounds which share the structure of formulas I would not work as claimed.

As indicated above, the burden is on the Patent Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. On the present record there is no such explanation, and no apparent reason is offered to support the notion that the statements in the specification are not true or accurate.

For the foregoing reasons, a person of skill in the art would be able to practice the claimed invention without further undue experimentation. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 1, 27, 36 – 42, 47, 51 and 52 under 35 U.S.C. 112, second paragraph, as indefinite, is respectfully traversed.

Claim 1 is amended to replace "R^{1b} and R^{2a}" with "R^1 and R^2" as kindly suggested by the Examiner.

In claims 27 and 36, the term "producing" is replaced with the term "preparing" as kindly suggested by the Examiner.

The Office Action alleges claims 27 and 36 are indefinite because they do not articulate whether the compounds of formulae II, III and IV are reacted separately or simultaneously with trifluoroacetic acid.

The relevant question is whether one of skill in the art could understand the scope of the claim. The MPEP states that:

> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000).

In the present case, that test is clearly met, because one of skill in the art would readily understand the scope of the claims. The law of definiteness does not burden patent applicants with alternative choices, such as selecting between simultaneous and separate reactions. Accordingly, the claims meet the requirements for definiteness under the law.

Claims 37 and 40 are amended to make them dependent from process claim 27 rather than compound claim 25. Accordingly, claims 37-42 are provided proper antecedent basis for the terminology therein.

The term –alleviating– in claim 47 is not indefinite for failure to provide a degree of alleviation. As described above, the term alleviate simply means to lessen and any degree of alleviation, i.e., any lessening of the pain, would amount to alleviating as is claimed. Although there are a variety of ways to measure pain known to persons of skill in the art (and alleviation would amount a to difference in perceived pain), the method of assessing alleviation is not important to the present claims, since they encompass any lessening of pain. Thus, the relevant question is whether or not pain there is <u>any</u> pain lessening rather than the degree of lessening achieved. The scope of the claim can thus be readily determined by a person of skill in the art. A person of skill in the art would be able to determine whether pain is lessened and whether some activity falls within the scope of the claim.

In claims 51 and 52, the term –inhibiting– is not indefinite for failure to provide a degree of inhibition. As with the term –alleviating–, the relevant question is whether or not there is any inhibition, not whether a particular amount of inhibition is achieved. The scope of the claim can thus be readily determined by a person of skill in the art. A the person of skill in the art would be able to determine whether any inhibition is achieved and whether some activity falls within the scope of the claim.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

35 U.S.C. 102

The rejection of claims 1 – 9, 11 and 15 – 24 under 35 U.S.C. 102(b) over Borrione (J. Chem. Soc. Perkin Trans.) is respectfully traversed.

The Office Action asserts that compounds 2a-d, 3a-d, 4a-d and 5a-d on page 2246 are relevant when R3 represents cycloalkyl. As amended, the claims are directed to the salt of the compound of formula I formed with a base. Borrione does not appear to teach this compound. Accordingly, the reference does not teach each and every element of the claimed invention and reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 1-24 under 35 U.S.C. 102(b) over Kobayashi et al., J. Comb. Chem. 2:438-440 (2000) is respectfully traversed.

The Office Action refers to the various compounds 8 in scheme 2 on page 439. As indicated above, the claims are directed to the salt of the compound of formula I formed with a base. Kobayashi (2000) does not appear to teach this compound. Accordingly, the reference does not teach each and every element of the claimed invention and reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 1-24 under 35 U.S.C. 102(a) over Kobayashi et al., J. Comb. Chem. 3:196-204 (2001) is respectfully traversed.

The Office Action refers to compounds 14a, 14b, 14d and 14h on page 199. As indicated above, the claims are directed to the salt of the compound of formula I formed with a base. Kobayashi (2001) does not appear to teach this compound. Accordingly, the reference does not teach each and every element of the claimed invention and reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 1-52 under 35 U.S.C. 102(e) over Gerlach (U.S. Patent No. 6,699,877) is respectfully traversed.

Under § 102(e)(2), a patent granted on an application for patent by another may be prior art if that application is filed in the U.S. before the applicant's date of invention, provided that an international application may only serve as an application filed in the U.S. if the international application designated the U.S. and was published in the English language.

In the present case, the '877 patent published as PCT application no. PCT/EP01/00588 in German rather than English. Accordingly, the PCT publication is not available as a reference under 102(e)(2). The application that issued as the '877 patent was published in the U.S. as U.S. 2003/0087926, and this application was filed August 7, 2002.

The international application from which the present application claims priority, PCT/EP02/08729, was filed on August 5, 2002. Accordingly, this international application predates the filing of the application that issued as the '877 patent. As a result, the filing date of the application that issued as the '877 necessarily postdates the date of invention of the present application. Therefore, the rejection under 35 U.S.C. 102(e) cannot be properly maintained and reconsideration and withdrawal thereof are respectfully requested.

Double Patenting

Applicants file herewith a terminal disclaimer of U.S. Patent No. 6,699,877, therefore rendering moot the rejection of claims 1 – 52 as obvious over claims 1 – 62 of U.S. Patent No. 6,699,877. Withdrawal of that rejection is respectfully requested.

CONCLUSION

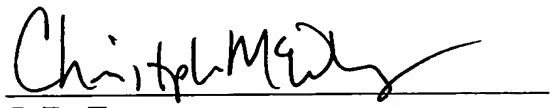
In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029310.53175US).

Respectfully submitted,

January 30, 2006



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APPENDIX A

Merriam-Webster Online Dictionary

Thesaurus

One entry found for **alleviate**.

Main Entry: **al·le·vi·ate**
Pronunciation: `&-'lE-vE-"At`
Function: *transitive verb*
Inflected Form(s): **-at·ed; -at·ing**
Etymology: Late Latin *alleviatus,* past participle of *alleviare,* from Latin *ad-* + *levis* light -- more at LIGHT
: RELIEVE, LESSEN: as **a :** to make (as suffering) more bearable <her sympathy *alleviated* his distress> **b :** to partially remove or correct
synonym see RELIEVE
- **al·le·vi·a·tion** /-"lE-vE-'A-sh&n/ *noun*
- **al·le·vi·a·tor** /-'lE-vE-"A-t&r/ *noun*

For **More Information on "alleviate" go to Britannica.com**
Get the **Top 10 Search Results for "alleviate"**

Pronunciation Symbols

ARTFL Project: Webster Dictionary, 1913

Searching for: **alleviate**
Found **1 hit(s).**

Alleviate (Page: 40)

Al*le"vi*ate (#), v. t. [imp. & p. p. Alleviated; p. pr. & vb. n. Alleviating.] [LL. alleviare, fr. L. ad + levis light. See Alegge, Levity.]

1. To lighten or lessen the force or weight of. [Obs.]

> Should no others join capable to **alleviate** the expense. *Evelyn.*
>
> Those large bladders . . . conduce much to the **alleviating** of the body [of flying birds]. *Ray.*

2. To lighten or lessen (physical or mental troubles); to mitigate, or make easier to be endured; as, to alleviate sorrow, pain, care, etc. ; -- opposed to *aggravate.*

> The calamity of the want of the sense of hearing is much **alleviated** by giving the use of letters. *Bp. Horsley.*

3. To extenuate; to palliate. [R.]

> He **alleviates** his fault by an excuse. *Johnson.*

Syn. -- To lessen; diminish; soften; mitigate; assuage; abate; relieve; nullify; allay. -- To Alleviate, Mitigate, Assuage, Allay. These words have in common the idea of relief from some painful state; and being all figurative, they differ in their application, according to the image under which this idea is presented. *Alleviate* supposes a load which is lightened or taken off; as, to alleviate one's cares. *Mitigate* supposes something fierce which is made mild; as, to mitigate one's anguish. *Assuage* supposes something violent which is quieted; as, to assuage one's sorrow. *Allay* supposes something previously excited, but now brought down; as, to allay one's suffering or one's thirst. To *alleviate* the distresses of life; to *mitigate* the fierceness of passion or the violence of grief; to *assuage* angry feeling; to *allay* wounded sensibility.

THIRD COLLEGE EDITION

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OF AMERICAN ENGLISH

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< LL *allegorizare*: see fol. & -IZE] 1 to make into or treat as an allegory 2 to interpret in an allegorical sense —*vi.* to make or use allegories —**al·le·gor·i·za·tion** (al'ə gôr'i zā'shən) *n.*

al·le·go·ry (al'ə gôr'ē) *n., pl.* **-ries** [ME *allegorie* < L *allegoria* < Gr *allēgoria*, description of one thing under the image of another < *allos*, other (see ELSE) + *agoreuein*, to speak in assembly < *agora*, AGORA¹] 1 a story in which people, things, and happenings have a hidden or symbolic meaning: allegories are used for teaching or explaining ideas, moral principles, etc. 2 the presenting of ideas by means of such stories; symbolic narration or description 3 any symbol or emblem

al·le·gret·to (al'ə gret'ō, ä'lə-) *adj., adv.* [It, dim. of *allegro*: see fol.] *Musical Direction* moderately fast; faster than *andante* but slower than *allegro* —*n., pl.* **-tos** an allegretto movement or passage

al·le·gro (ə le'grō', -lā'-) *adj., adv.* [It < L *alacer*, brisk, sprightly, cheerful] *Musical Direction* fast; faster than *allegretto* but not so fast as *presto* —*n., pl.* **-gros** an allegro movement or passage

al·lele (ə lēl') *n.* [Ger *allel* < Gr *allēlōn*, of one another] either of a pair of genes located at the same position on both members of a pair of chromosomes and conveying characters that are inherited in accordance with Mendelian law —**al·lel·ic** (ə lēl'ik, -lel'-) *adj.* —**al·lel'ism** (-lēl'iz'əm, -lel'-) *n.*

al·le·lo·morph (ə lēl'ō môrf', ə lel'ō-) *n.* [< prec. + -MORPH] ALLELE —**al·lel'o·mor'phic** *adj.*

al·lel·op·a·thy (al'əl äp'ə thē, al'ēl-) *n.* the repression or destruction of plants from the effect of certain toxic chemical substances produced and released by other, nearby plants —**al·le·lo·path·ic** (ə lēl'ō path'ik, -lel'-) *adj.*

al·le·lu·ia (al'ə lōō'yə, ä'lə-; ä'lä lōō'yä') *interj., n.* [LL(Ec) < Gr *allēlouia* < Heb *haleluya*, HALLELUJAH] HALLELUJAH

al·le·mande (al'ə mand', -mänd') *n.* [Fr < *allemand*, German < OFr *aleman* < ML *Alemannus*: see ALEMANNI] 1 a German dance of the 16th century in moderate duple time 2 a stylized instrumental composition evolved from this dance and often used as the first movement of a Baroque suite 3 a figure in a square dance in which two dancers join right or left hands and make a turn

Al·len (al'ən) 1 a masculine name: see ALAN 2 **Ethan** 1738-89; Am. Revolutionary soldier who led the Green Mountain Boys in the capture of Fort Ticonderoga

Al·len·by (al'ən bē), **Edmund Henry Hyn·man** (hin'mən) 1st Viscount 1861-1936; Brit. army officer: commander of Brit. expeditionary forces in Egypt (1917-1918); high commissioner of Egypt (1919-25)

Al·len·town (al'ən toun') [after Wm. *Allen*, the founder] city in E Pa., on the Lehigh River: pop. 104,000 (met. area, incl. Bethlehem & Easton, 637,000)

Allen wrench [*often* **a-** w-] a thin, L-shaped wrench with a hexagonal head at both ends, designed to fit the sockets of certain screws and bolts

☆al·ler·gen (al'ər jən, -jen') *n.* [Ger < *allergie*, ALLERGY + *-gen*, -GEN] a substance inducing an allergic state or reaction —**al'ler·gen'ic** (-jen'ik) *adj.*

☆al·ler·gic (ə lur'jik) *adj.* 1 of or caused by allergy 2 having an allergy 3 [Colloq.] averse or disinclined (*to*) *[allergic to study]*

☆al·ler·gist (al'ər jist) *n.* a doctor who specializes in treating allergies

☆al·ler·gy (al'ər jē) *n., pl.* **-gies** [Ger *allergie* < Gr *allos*, other (see ELSE) + *-ergeia*, as in *energeia* (see ENERGY)] 1 a hypersensitivity to a specific substance (such as a food, pollen, dust, etc.) or condition (as heat or cold) which in similar amounts is harmless to most people: it is manifested in a physiological disorder 2 a strong aversion

☆al·le·thrin (al'ə thrin') *n.* [< *all(ene)* < *allylene* (< ALLYL + -ENE) + (PYR)ETHR(UM) + -IN¹] a thick, pale yellow, synthetic liquid insecticide, $C_{19}H_{26}O_3$, similar in structure to pyrethrin

al·le·vi·ate (ə lē'vē āt') *vt.* **-at·ed, -at·ing** [ME *alleviaten* < LL *alleviatus*, pp. of *alleviare*; for L *allevare* < *ad-*, to + *levis*, LIGHT²] 1 to make less hard to bear; lighten or relieve (pain, suffering, etc.) 2 to reduce or decrease *[to alleviate poverty]* —*SYN.* RELIEVE —**al·le'vi·a'tor** *n.* —**al·le'vi·a·tive** or **al·le'vi·a·to'ry** (-ə tôr'ē) *adj.*

al·le·vi·a·tion (ə lē'vē ā'shən) *n.* 1 an alleviating or being alleviated 2 a thing that alleviates

al·ley¹ (al'ē) *n., pl.* **-leys** [ME *aly* < OFr *alee* < *aler* (Fr *aller*), to go < ML *alare*, contr. < L *ambulare*, to walk: see AMBLE] 1 a lane in a garden or park, bordered by trees or shrubs 2 a narrow street or walk; specif., a lane between or behind buildings or rows of buildings 3 *Bowling* LANE¹ (senses 6*a* & *b*) 4 *Tennis* either of the narrow lanes, on opposite sides of the court, that extend the singles area for playing doubles —**☆up (or down) one's alley** [Slang] suited to one's tastes or abilities

al·ley² (al'ē) *n., pl.* **-leys** [< ALABASTER, formerly used for marbles] a fine marble used as the shooter in playing marbles

☆alley cat a homeless, mongrel cat

al·ley-oop (al'ē o͞op') *interj.* [< Fr *allez* (imper. of *aller*, to go), used as interj. of encouragement, surprise, exhortation + *oop* < ?] an exclamation accompanying the act of lifting, rising, etc. —*n. Basketball* a high, lobbed pass to a teammate near the basket who attempts a slam-dunk or a tip-in

☆al·ley·way (al'ē wā') *n.* 1 an alley between buildings 2 any narrow passageway

all-fired (ôl'fīrd') *adj.* [altered < *hell-fired*] [Slang] extreme; complete —*adv.* [Slang] extremely; completely

All Fools' Day APRIL FOOLS' DAY

all fours any of several card games in which four points may be scored during the play of a hand, for winning the high trump, low trump, and jack of trumps, and for "game" (the largest high-card count): see also phrase ON ALL FOURS (at FOUR)

all hail [Archaic] all health: a greeting

All·hal·lows (ôl'hal'ōz') *n.* [ME *alhalwes* < OE *ealra halgena (dæg)*, see ALL & HALLOW¹] [Archaic] ALL SAINTS' DAY Also called **All·hal·low·mas** (-hal'ō məs)

All-hal·low-tide (-hal'ō tīd') *n.* [ME *alle halwen tid*: see prec. & TIDE¹] [Archaic] the time or season of Allhallows

all-heal (ôl'hēl') *n.* any of various plants, as selfheal or valerian, thought to have medicinal properties

al·li·a·ceous (al'ē ā'shəs) *adj.* [< L *allium*, garlic + -ACEOUS] 1 of a group of strong-smelling bulb plants of the lily family, including the onion, garlic, etc. 2 having the smell or taste of onions or garlic

al·li·ance (ə lī'əns) *n.* [ME *aliaunce* < OFr *aleiance* < *aliers*: see ALLY] 1 an allying or being allied; specif., a union or joining, as of families by marriage 2 a close association for a common objective, as of nations, political parties, etc. 3 the agreement made for such an association 4 the countries, groups, etc. forming such a connection 5 similarity or relationship in characteristics, structure, etc.; affinity

***SYN.*—alliance** refers to any association entered into for mutual benefit; **league**, often interchangeable with **alliance**, stresses formality of organization and definiteness of purpose; **coalition** implies a temporary alliance of opposing parties, etc., as in times of emergency; **confederacy** and **confederation** in political usage refer to a combination of independent states for the joint exercise of certain governmental functions, as defense or customs; **union** implies a close, permanent alliance and suggests complete unity of purpose and interest

al·li·cin (al'ə sin') *n.* [< *allium*, an amino acid found in garlic oil (< L *allium*, garlic + -IN¹) + -(i)C + -IN¹] an unstable, yellowish, oily liquid, $C_6H_{10}OS_2$, extracted from garlic and used as an antibacterial substance in science and industry

al·lied (ə līd'; *also, esp. for 3*, al'īd') *adj.* [see ALLY] 1 united by kinship, treaty, agreement, etc. 2 closely related /Danish and Swedish are *allied* languages/ 3 [**A-**] of the Allies —*SYN.* RELATED

Al·lier (al yā') river in central France, flowing northward into the Loire: c. 250 mi. (402 km)

Al·lies (al'īz', ə līz') *n.pl.* 1 in World War I, the nations allied by treaty against Germany and the other Central Powers; orig., Great Britain, France, and Russia, later joined by the U.S., Italy, Japan, etc. 2 in World War II, the nations associated against the Axis, esp. Great Britain, the Soviet Union, and the U.S.: see UNITED NATIONS

al·li·ga·tor (al'ə gāt'ər) *n., pl.* **-tors** or **-tor** [Sp *el lagarto* < *el*, the + L *lacerta*, *lacertus*: see LIZARD] 1 any of a genus (*Alligator*) of large crocodilian reptiles found in tropical rivers and marshes of the U.S. and China: its snout is shorter and blunter than the crocodile's, and its teeth do not protrude outside its closed mouth 2 a scaly leather made from an alligator's hide ☆3 a machine, tool, etc. with a strong, movable, often toothed jaw

alligator pear [altered (? by folk etym. because of the appearance of the skin) < *avogato*: see AVOCADO] AVOCADO

☆alligator snapper a large, freshwater snapping turtle (*Macroclemys temminckii*) of the SE U.S. and the Mississippi Valley, found chiefly in rivers and bayous: it may weigh up to 100 kg (220 lbs.)

all-important (ôl'im pôrt'ənt) *adj.* highly important; necessary; essential

all-inclusive (-in klōō'siv) *adj.* including everything; comprehensive

al·lit·er·ate (ə lit'ər āt') *vi.* **-at·ed, -at·ing** [back-form. < fol.] 1 to constitute or show alliteration 2 to use alliteration —*vt.* to cause to show alliteration

al·lit·er·a·tion (ə lit'ər ā'shən) *n.* [ML *alliteratio* < L *ad-*, to + *littera*, LETTER¹] repetition of an initial sound, usually of a consonant or cluster, in two or more words of a phrase, line of poetry, etc. (Ex.: "What a tale of terror now their turbulency tells!")

al·lit·er·a·tive (ə lit'ər āt'iv, -ər ə tiv) *adj.* of, showing, or using alliteration —**al·lit'er·a·tive·ly** *adv.*

al·li·um (al'ē əm) *n.* [ModL < L, garlic] any strong-smelling bulb plant of a genus (*Allium*) of the lily family, as the onion, garlic, leek, etc.

all-nighter (ôl'nīt'ər) *n.* [Colloq.] something that lasts through the night, as a work or study session or a party

al·lo- (al'ō, al'ə) [< Gr *allos*, other: see ELSE] *combining form* variation; departure from the normal, reversal *[allonym, allomorph]*

al·lo·cate (al'ō kāt', al'ə-) *vt.* **-cat·ed, -cat·ing** [< ML *allocatus*, pp. of *allocare* < L *ad-*, to + *locare*, to place < *locus*: see LOCUS] 1 to set apart for a specific purpose *[to allocate* funds for housing*]* 2 to distribute in shares or according to a plan; allot 3 to fix the location of; locate —*SYN.* ALLOT —**al·lo·ca·ble** (al'ə kə bəl) or **al'lo·cat·a·ble** *adj.*

al·lo·ca·tion (al'ō kā'shən, al'ə-) *n.* 1 an allocating or being allocated 2 a thing or amount allocated

al·loch·tho·nous (ə läk'thə nəs) *adj.* [ALLO- + (AUTO)CHTHON + -OUS] originating elsewhere; not native to a place

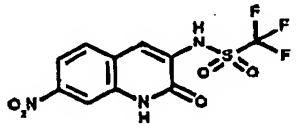
al·lo·cu·tion (al'ō kyōō'shən, al'ə-) *n.* [L *allocutio* < *alloqui*, to speak

APPENDIX B

NEURONAL INJURY INHIBITORS

196910

7-Nitro-3-(trifluoromethylsulfonamido)quinolin-2(1*H*)-one



C10-H6-F3-N3-O5-S ; Mol wt: 337.23

ACTION - Neuronal injury inhibitor with a dual mechanism of action; it antagonizes both AMPA/kainate and NMDA/glycine receptors, with K_i values lower than 1 mcM and a ratio of K_i AMPA/K_i NMDA of 0.60 in Xenopus oocyte preparations. A specifically claimed compound within a series of 3-sulfonylamino-2(1*H*)-quinolinone derivatives.

SOURCE - ADIR.

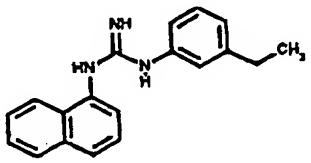
REFERENCES

1 Corbi, A. et al. (ADIR et Cie.) *3-Sulfonylamino2(1H)-quinolinones and 7-aza derivs. as excitatory amino acids antagonists.* EP 542609, FR 2683816.

CNS-1086

199617

N^1-(3-Ethylphenyl)-*N*^{3}-(1-naphthyl)guanidine



C19-H19-N3 ; Mol wt: 289.38

ACTION - Potential neuroprotective agent related to CNS-1102*, NMDA receptor antagonist that acts as an ion channel blocker, as demonstrated in binding studies using [^{3}H]-MK-801 (IC_{50} = 38.6 nM).

SOURCE - Cambridge NeuroScience.

REFERENCES

1. Goldin, S.M. et al. (Cambridge NeuroScience, Inc.) *Substd. guanidines and derivs. thereof as modulators of neurotransmitter release and novel methodology for identifying neurotransmitter release blockers.* WO 9214697.

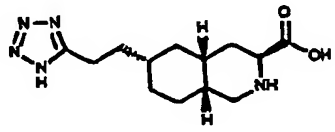
2. Hu, L.-Y. et al. *Synthesis and structure–activity studies of N-(1-naphthyl)-N'-(3-ethylphenyl)-N'-methylguanidine analogs (CNS 1102 analogs) for NMDA-ion-channel blockade.* 206th ACS Natl Meet (Aug 22-27, Chicago) 1993. Abst MEDI 164

* Annu Drug Data Rep 1991, 13(11): 933

LY-215490

199333

(±)-(3*S**,4a*R**,6*R**,8a*R**)-6-[2-(1*H*-Tetrazol-5-yl)-ethyl]decahydroisoquinoline-3-carboxylic acid



C13-H21-N5-O2 ; Mol wt: 279.34

ACTION - Potent, competitive, selective and systemically active AMPA receptor antagonist, that showed an IC_{50} of 4.81 ± 1.23 mcM for displacement of [^{3}H]-AMPA binding in rat cortical slices, compared to respective values of 26.4 ± 1.9 and 247 ± 8 mcM for displacement of [^{3}H]-CGS-19755 (NMDA receptors) and [^{3}H]-kainic acid binding, with no affinity for glycine receptors. Compound antagonized AMPA-induced depolarizations in rat cortical slices with an IC_{50} of 6.0 ± 1.0 mcM and a pA_2 of 6.37 ± 0.02, being 5- to 10-fold less potent against kainic acid- and NMDA-induced depolarizations. In *in vivo* assays, it induced dose-dependent inhibition of AMPA-induced rigidity in mice (ED_{50} = 3.6 mg/kg i.p. 30 min before testing) and blocked maximal electroshock seizures in mice (ED_{50} = 9.0 mg/kg i.p. 30 min before testing), with no effect on NMDA-induced lethality and disruption in the horizontal screen assay at higher doses (ED_{50} = 19.6 mg/kg i.p. 30 min before testing), indicating a good separation between therapeutic doses and those producing side effects.

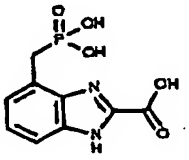
SOURCE - Lilly.

REFERENCES

1 Ornstein, P.L. et al. *(3SR,4aRS,6RS,8aRS)-6-[2-(1H-Tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid: A structurally novel, systemically active, competitive AMPA receptor antagonist.* J Med Chem 1993, 36(14), 2048

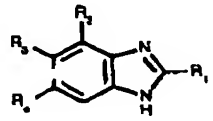
198235

4-(Phosphonomethyl)-1*H*-benzimidazole-2-carboxylic acid



C9-H9-N2-O5-P ; Mol wt: 256.15

ACTION - Agent for the treatment of neurotoxic injury associated with anoxia or ischemia following stroke, cardiac arrest or perinatal asphyxia; an NMDA receptor antagonist with a K_i = 1.6 mcM in the [^{3}H]-glutamate binding assay, whereas K_i was > 100 mcM when using [^{3}H]-kainate as the ligand. Significant *in vivo* antiischemic activity was demonstrated in a gerbil forebrain ischemia assay when given intraperitoneally at doses of 300 and 500 mg/kg, 30 min prior to carotid occlusion. Compound also exhibited anticonvulsant activity, as demonstrated by inhibiting electroconvulsive shock in mice and by protecting against motor function impairment at a dose of 56 mg/kg s.c. A representative compound from a wide series of specifically claimed diacid-containing benzimidazole derivatives, wherein the following are included:



200776: C10-H8-N10: R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2, R3 = R4 = H
200777: C11-H10-N10: R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2, R3 = Me, R4 = H
200778: C11-H9-Cl-N10: R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2CH2, R3 = H, R4 = Cl
200779: C9-H6-N10: R1 = R2 = 5-tetrazolyl, R3 = R4 = H
200780: C9-H11-N8-O-P: R1 = 5-tetrazolyl, R2 = CH2PO(NH2)2, R3 = R4 = H
200781: C10-H13-N8-O-P: R1 = 5-tetrazolyl, R2 = CH2PO(NH2)2, R3 = Me, R4 = H
200782: C10-H12-Cl-N8-O-P: R1 = 5-tetrazolyl, R2 = (CH2)2PO(NH2)2, R3 = H, R4 = Cl
200783: C10-H13-N8-O-P: R1 = 5-tetrazolyl, R2 = (CH2)2PO(NH2)2, R3 = R4 = H
200784: C11-H15-N8-O-P: R1 = 5-tetrazolyl, R2 = (CH2)3PO(NH2)2, R3 = R4 = H
200785: C11-H10-N2-O4: R1 = CO2H, R2 = CH2CO2H, R3 = Me, R4 = H
200786: C11-H10-N2-O4: R1 = CO2H, R2 = (CH2)2CO2H, R3 = R4 = H
200787: C12-H11-Cl-N2-O4: R1 = CO2H, R2 = (CH2)3CO2H, R3 = H, R4 = Cl
200788: C9-H6-N2-O4: R1 = R2 = CO2H, R3 = R4 = H
200789: C10-H8-N2-O4: R1 = R2 = CO2H, R3 = Me, R4 = H

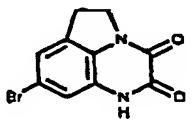
SOURCE - Searle.

REFERENCES

1 Vazquez, M.L. (G.D. Searle & Co.) *Diacid-containing benzimidazole cpds. for treatment of neurotoxic injury.* US 5216003

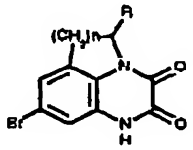
197041

8-Bromo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione



C10-H7-Br-N2-O2 : Mol wt: 267.08

ACTION - Agent for the prevention and treatment of neurodegenerative disorders, a selective antagonist of glutamate receptors which strongly inhibits both [^{3}H]-MK-801 binding and [^{3}H]-glycine binding to the rat brain synaptic membrane preparation. Also claimed for its use as analgesic, antidepressant, anxiolytic or antipsychotic agent. A compound within a wide series of exemplified tricyclic quinoxalinedione derivatives, wherein the following are included:



200083: C11-H7-Br-N2-O4: R = CO2H, n = 1
200084: C18-H14-Br-N3-O3: R = CONHCH2Ph, n = 1
200085: C19-H16-Br-N3-O3: R = CONHCH2CH2Ph, n = 1
200086: C11-H10-Br-N3-O2: R = CH2NH2, n = 1
200087: C13-H11-Br-N2-O4: R = CH2CO2Me, n = 1
200088: C12-H9-Br-N2-O4: R = CH2CO2H, n = 1
200089: C19-H16-Br-N3-O3: R = CH2CONHCH2Ph, n = 1
200090: C17-H13-Br-N4-O3: R = NHCONHPh, n = 1
200091: C13-H11-Br-N2-O4: R = CO2Me, n = 2
200092: C12-H9-Br-N2-O4: R = CO2H, n = 2
200093: C19-H16-Br-N3-O3: R = CONHCH2Ph, n = 2
200094: C20-H18-Br-N3-O3: R = CONHCH2CH2Ph, n = 2
200095: C14-H13-Br-N2-O4: R = CH2CO2Me, n = 2
200096: C12-H10-Br-N3-O3: R = CONH2, n = 2
200097: C12-H12-Br-N3-O2: R = CH2NH2, n = 2

SOURCE - Sumitomo.

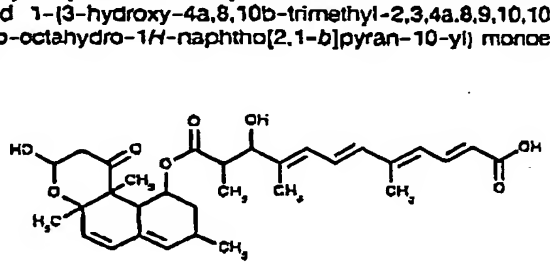
REFERENCES

1 Nagata, R. et al. (Sumitomo Pharm. Co. Ltd.) *Tricyclic quinoxalinediones as glutamate receptor antagonists.* JP 93117276, WO 9308186

NG-111

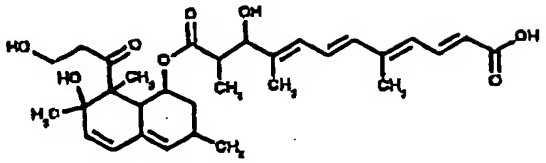
196611

3-Hydroxy-2,4,8-trimethyldodeca-4,6,8,10-tetraenedioic acid 1-(3-hydroxy-4a,8,10b-trimethyl-2,3,4a,8,9,10,10a,10b-octahydro-1*H*-naphtho[2,1-*b*]pyran-10-yl) monoester



C31-H40-O8 : Mol wt: 540.65

ACTION - Cerebroprotective agent isolated from *Aspergillus versicolor* F5015, which promotes the production of nerve growth factor (NGF) by 225% at 0.03 mcg/ml in mouse fibroblasts. Potentially useful for the treatment of dementia. Another specifically claimed decalin derivative is:



NG-112 [200114]: C31-H42-O8

SOURCE - Taisho.

REFERENCES

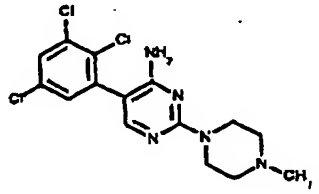
1 Nomura, K. et al. (Taisho Pharm. Co., Ltd.) *Decalin-type cpds.* JP 93032656

BW-619C89*

164985

4-Amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)pyrimidine

2-(4-Methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)pyrimidine-4-amine



C15-H16-Cl3-N5 ; Mol wt: 372.68

ACTION - Cerebroprotective agent, pyrimidine analog of BW-1003C87*, that potently and selectively inhibited veratrine-induced release of glutamate and aspartate from rat cerebral cortex slices (IC_{50} = 5.3 and 5.1 mcM, respectively). It induced marked decreases in both total and cortical infarct volumes in rats with permanent middle cerebral artery occlusion, with maximum decreases of about 60% at 30 mg/kg I.v.; behavioral effects of body tremor and ataxia were generally minor. It is suggested that glutamate release inhibitors such as title compound may provide an alternative to excitatory amino acid receptor antagonists in the treatment of focal cerebral ischemia and stroke.

SOURCE - Wellcome.

REFERENCES

1 Miller, A.A. et al. (The Wellcome Found., Ltd.) *Pharmacologically active CNS cpds.* AU 8945984, EP 372934, JP 90202678

2 Leach, M.J. et al. (The Wellcome Found., Ltd.) *Pharmacologically active CNS cpds.* EP 459812**

3 Leach, M.J. and Nobbs, M.S. (The Wellcome Found., Ltd.) *Pharmacologically active CNS cpds.* EP 459830***.

4 Leach, M.J. et al. *BW619C89, a glutamate release inhibitor, protects against focal cerebral ischemic damage.* Stroke 1993, 24(7): 1063.

*Identified compound 164985 (see 163727) Annu Drug Data Rep 1990, 12(10): 773

**See 179264 Annu Drug Data Rep 1992, 14(6): 495

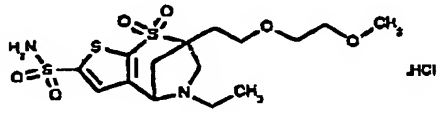
***See 179245 Annu Drug Data Rep 1992, 14(6): 496

*Annu Drug Data Rep 1993, 15(4): 312

ANTIGLAUCOMA AGENTS

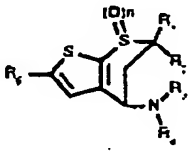
197566

4-Ethyl-2-[2-(2-methoxyethoxy)ethyl]-2,3,4,5-tetrahydro-2,5-methanothieno[3,2-*f*]-1,4-thiazepine-7-sulfonamide 1,1-dioxide hydrochloride



C15-H24-N2-O6-S3.HCl ; Mol wt: 461.01

ACTION - Antiglaucoma agent, inhibitor of carbonic anhydrase; for topical ocular administration. Other specifically claimed tricyclic thienothiopyran derivatives include the following:



199747: C18-H22-N2-O5-S3: R1 = Me, R2,R3 = -CH2CH2-, R4 = 4-MeO-PhCH2, R5 = SO2NH2, m = 2

199748: C21-H28-N2-O6-S3: R1 = (CH2)3OMe, R2,R3 = -CH2CH2-, R4 = 4-MeO-PhCH2, R5 = SO2NH2, m = 2

199749: C10-H14-N2-O4-S3.HCl: R1 = Me, R2,R3 = -CH2CH2-, R4 = H, R5 = SO2NH2, m = 2, hydrochloride

199750: C13-H19-N-O-S2: R1 = (CH2)3OMe, R2,R3 = -CH2CH2-, R4 = R5 = H, m = 0

199751: C13-H18-N2-O3-S3: R1 = H, R2,R3 = -CH2CO-, R4 = *i*-Bu, R5 = SO2NH2, m = 0

199752: C13-H18-N2-O5-S3: R1 = H, R2,R3 = -CH2CO-, R4 = *i*-Bu, R5 = SO2NH2, m = 2

199753: C13-H20-N2-O4-S3.HCl: R1 = H, R2,R3 = -CH2CH2-, R4 = *i*-Bu, R5 = SO2NH2, m = 2, hydrochloride

199754: C12-H18-N2-O4-S3.HCl: R1 = H, R2,R3 = -CH2CH2-, R4 = Pr, R5 = SO2NH2, m = 2, hydrochloride

199755: C11-H16-N2-O4-S3.HCl: R1 = H, R2,R3 = -CH2-, R4 = Pr, R5 = SO2NH2, m = 2, hydrochloride

199756: C10-H14-N2-O4-S3.HCl: R1 = H, R2,R3 = -CH2-, R4 = Et, R5 = SO2NH2, m = 2, hydrochloride, (*S,S*)-isomer

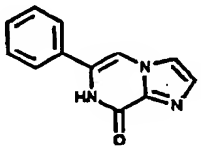
SOURCE - Merck & Co.

REFERENCES

1 Baldwin, J.J. et al. (Merck & Co., Inc.) *Tricyclic thienothiopyrans as antiglaucoma agents.* EP 543497

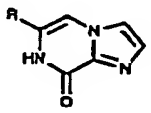
225249

6-Phenylimidazo[1,2-*a*]pyrazin-8(7*H*)-one



C12-H9-N3-O ; Mol wt: 211.22

ACTION – Noncompetitive antagonist at the glycine site of the NMDA receptor, potentially useful for the treatment and prophylaxis of cerebral ischemic/anoxic disorders, and for the treatment of neurodegenerative disorders such as parkinsonism and Alzheimer's disease, as well as epilepsy, schizophrenia and migraine. Other exemplified imidazopyrazinones include the following:



227609; C12-H8-Cl-N3-O: R= 4-Cl-Ph
227610; C12-H7-Cl2-N3-O: R= 3,4-(Cl)2-Ph
227611; C11-H8-N4-O: R= 2-Pyr
227612; C10-H7-N3-O2: R= 2-furyl

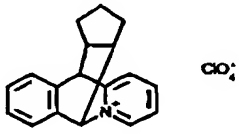
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Alsop, J.-C. et al. (Rhône-Poulenc Rorer SA) *7H-Imidazo(1,2-a)pyrazine-8-one NMDA receptor antagonists.* WO 9512594.

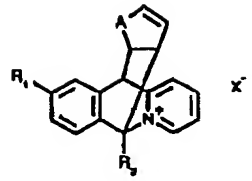
226638

11,12,13,14,15,16-Hexahydro-6*H*-6,11[1',2']cyclopentabenzo[*b*]quinolizinium perchlorate



C18-H18-Cl-N-O4 ; Mol wt: 347.80

ACTION – Neuroprotective agent that binds to the phencyclidine (PCP) receptor (K_i = 366 nM against binding of [^{3}H]-TCP in rat brain preparations), and thus acts as a noncompetitive antagonist of the NMDA receptor. Compound antagonized NMDA-induced neurotoxicity in cultured fetal mouse cortical neurons (IC_{50} = 8400 nM). A compound within a series of 6,11-substituted-6,11-dihydrobenzo-[*b*]quinolizinium salts, wherein the following are also included:



228143; C19-H18-Br-N: R1=R2= H, A= CH2CH2, X= Br
228144; C18-H15-Br-N: R1= Br, R2= H, A= CH2, X= Br
228145; C18-H15-Cl-F-N-O4: R1= F, R2= H, A= CH2, X= ClO4
228146; C19-H18-Cl-N-O4: R1= H, R2= Me, A= CH2, X= ClO4
228147; C21-H21-Cl-N-O4: R1=R2= H, A= C(Me)2=C, X= ClO4
228148; C18-H16-Br-N: R1=R2= H, A= CH2, X= Br

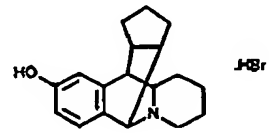
SOURCE – Sterling Winthrop.

REFERENCES

1. DeHaven-Hudkins, D.L. and Mattamo, J.P. (Sterling Winthrop, Inc.) *6,11-Substd.-6,11-dihydrobenzo[b]quinolizinium salts and compsns. and method of use thereof.* US 5430056.

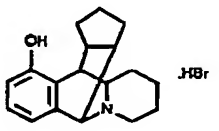
226654

9-Hydroxy-1,2,3,4,6,11,11a,12,13,14,15,16-dodecahydro-6,11[1',2']cyclopentabenzo[*b*]quinolizine hydrobromide



C18-H23-N-O.HBr ; Mol wt: 350.30

ACTION – Neuroprotective agent that potently binds to the phencyclidine (PCP) receptor (K_i = 2.31 nM against [^{3}H]-TCP binding in rat brain preparations), and thus acts as a noncompetitive antagonist of the NMDA receptor. Compound showed an IC_{50} of 42 nM for inhibition of NMDA-induced neurotoxicity in cultured fetal mouse brain neurons. Another specifically claimed 6,11-cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[*b*]quinolizine is:



228142; C18-H23-N-O.HBr

SOURCE – Sterling Winthrop.

REFERENCES

1. DeHaven-Hudkins, D.L. et al. (Sterling Winthrop, Inc.) *6,11-Cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[b]quinolines and compsns. and method of use thereof.* US 5434159.

HEK4BP

239917

Polypeptide that binds to the HEK4 receptor

HEK4-binding protein

ACTION – HEK4 receptor-binding protein that binds to one or more of the EPH-like receptors, particularly the HEK4 receptor. The polypeptide is useful for modulating the growth and/or differentiation of a variety of tissues, for example, liver, kidney, lung, skin or neural tissue, and may be useful in the treatment of CNS disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and spinal cord injury, and for the regeneration of damaged tissues. Antagonists of this polypeptide may be useful in the treatment of cancer.

SOURCE – Amgen.

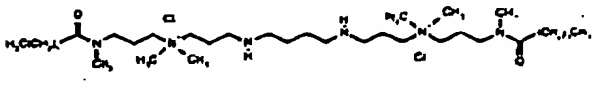
REFERENCES

1. Bartley, T.D. and Fox, G.M. (Amgen, Inc.) *Ligands for EPH-like receptors.* WO 9623000

YM-49635

240641

4,4,17,17-Tetramethyl-1,20-bis(*N*-methylundecanamido)-8,13-diaza-4,17-diazoniaeicosane dichloride



C44-H94-Cl2-N6-O2 ; Mol wt: 810.17

ACTION – Cognition-enhancing agent extracted from the sponge *Eylus* sp., with high affinity for the N-type calcium channel (IC_{50} = 5.8 µM against [^{125}I]-ω-conotoxin binding). Another tetraazaeicosane compound from this source is:

YM-49636 [241105]; C22-H54-Cl2-N6

SOURCE – Yamanouchi.

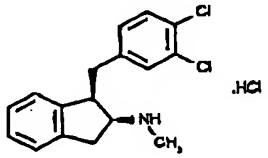
REFERENCES

1. Fushiya, N. et al. (Yamanouchi Pharm. Co., Ltd.) *Tetraazaeicosan cpds.* JP 96176083.

TREATMENT OF CEREBROVASCULAR DISEASES

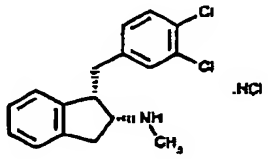
239793

(–)-*cis*-*N*-[1-(3,4-Dichlorobenzyl)indan-2-yl]-*N*-methylamine hydrochloride



C17-H17-Cl2-N.HCl ; Mol wt: 342.69

ACTION – Agent for the treatment of ischemic stroke, a single enantiomer of a known neuronal calcium antagonist proven to induce 99% inhibition of plateau Ca^{2+} current in superior cervical ganglion neurons (N-type calcium current) at a concentration of 5 µM. It is reported to significantly attenuate histological damage in cerebral ischemic models using gerbils and mice. The other single enantiomer is:



240451; C17-H17-Cl2-N.HCl: (+)-*cis*-isomer

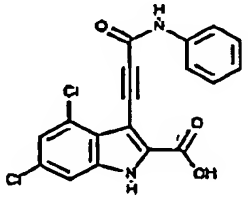
SOURCE – SmithKline Beecham.

REFERENCES

1. Odek, B.S. and Harling, J.D. (SmithKline Beecham plc) *Enantiomers of 1-(3,4-dichlorobenzyl)-2-methylaminoindane.* WO 9621641.

240624

4,6-Dichloro-3-(*N*-phenylcarbamoylethynyl)-1*H*-indole-2-carboxylic acid



C18-H10-Cl2-N2-O3 ; Mol wt: 373.19

ACTION – An NMDA antagonist acting at the strychnine-insensitive glycine binding site and structurally related to GV-150526, for use in the treatment of CNS disorders such as stroke, Huntington's disease, Alzheimer's disease and neurotrauma. Its affinity (pK_i = 7.7) is inferior to that of GV-150526 (pK_i = 8.5), but it displayed good *in vivo* activity in mice against NMDA-induced convulsions (ED_{50} = 0.2 mg/kg i.v.; ED_{50} GV-150526 = 0.06 mg/kg i.v.).

SOURCE – Glaxo Wellcome.

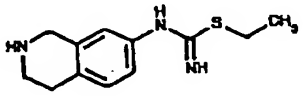
REFERENCES

1. Cuggia, A. and Gavtraghi, G. (Glaxo SpA) *Indole antagonists of excitatory amino acids.* BE 1006143, CH 685630, EP 555735, FR 2690919, GB 2266091, JP 94049027, US 5373018, US 5374648, US 5374649, WO 9321153.

2. Di Fabio, R. et al. *3-Alkynyl-2-carboxyindoles as a novel class of antagonists acting at the strychnine-insensitive glycine binding site.* 14th Int Symp Med Chem (Sept 9-12, Maastricht) 1996, Abst P-8.17.

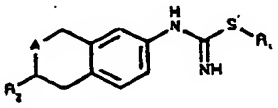
240961

N-(1,2,3,4-Tetrahydroisoquinolin-7-yl)carbamimidothioic acid ethyl ester



C12-H17-N3-S ; Mol wt: 235.35

ACTION – Agent for the treatment of neurodegenerative disorders that displays neuronal nitric oxide synthase (NOS)-inhibitory activity (IC_{50} < 10 µM); compound displayed a good level of selectivity as it inhibited inducible and endothelial forms of the enzyme at concentrations at least 10 times higher. Other specifically claimed bicyclic isothiourea derivatives include the following:



242637; C20-H24-Cl-N3-S: R1= Et, R2= 3-Cl-PhCH2N(Me), A= bond
242638; C14-H20-N2-S: R1= Et, R2= Me, A= CH2
242639; C13-H18-N2-S: R1=R2= Me, A= CH2

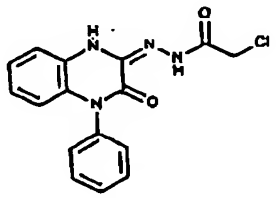
SOURCE – Astra.

REFERENCES

1. MacDonald, J.E. (Astra AB) *Bicyclic isothiourea derivs. useful in therapy.* WO 9624588.

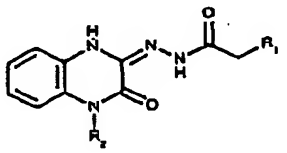
240999

2-Chloro-N^2-(3-oxo-4-phenyl-1,2,3,4-tetrahydroquinoxalin-2-ylidene)acetohydrazide



C16-H13-Cl-N4-O2 ; Mol wt: 328.76

ACTION – Agent for the treatment of neurodegenerative disorders, an inhibitor of both calpain I and calpain II (IC_{50} = 0.364 and 0.590 µM, respectively, using enzyme from human erythrocytes), with negligible inhibitory activity against other proteases such as cathepsin B, trypsin and thermolysin (IC_{50} > 200 µM). Compound proved effective in protecting against the toxic effects of AMPA to Purkinje cells in cerebellar slices, and against the effects of oxygen/glucose deprivation in fetal rat cortical cell cultures. Other specifically claimed α-substituted hydrazides include the following:



241510; C11-H11-Cl-N4-O2: R1= Cl, R2= Me
241511; C16-H13-Br-N4-O2: R1= Br, R2= Ph
241512; C16-H12-Cl2-N4-O2: R1= Cl, R2= 4-Cl-Ph

SOURCE – Warner-Lambert.

REFERENCES

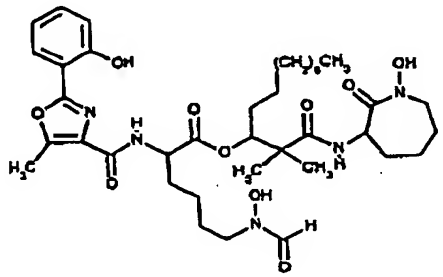
1. Wang, K.K.-W. and Yuen, P.-W. (Warner-Lambert Co.) *α-Substd. hydrazides having calpain inhibitory activity.* WO 9625403.

FORMOBACTIN

240625

6-(*N*-Hydroxyformamido)-2-[2-(2-hydroxyphenyl)-5-methyloxazol-4-ylcarboxamido]hexanoic acid 1-[1-[*N*-(1-hydroxy-2-oxoperhydroazepin-3-yl)carbamoyl]-1-methylethyl]decyl ester

ND-20



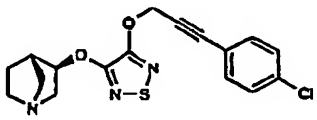
C38-H57-N5-O10 ; Mol wt: 743.90

White powder, m.p. 68-72 °C (decomp.), $[\alpha]_D^{25}$ –8.6° (c 1.0, MeOH).

ACTION – Neuroprotective agent and lipid peroxidation inhibitor isolated from the mycelium of *Nocardia* sp. ND20. It inhibited free radical-induced lipid peroxidation in rat brain homogenates with an IC_{50} of 0.65 µM, being more potent than butylated hydroxytoluene (BHT; IC_{50} = 1.80 µM). In addition, it protected against L-glutamate toxicity in neuronal hybridoma N18-RE-105 cells (EC_{50} = 0.017 µM) and inhibited buthionine sulfoximine-induced apoptosis in these cells (EC_{50} = 0.072 µM).

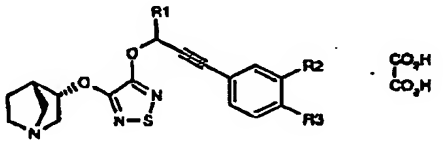
257732

(±)-*exo*-3-(1-Azabicyclo[2.2.1]hept-3-yloxy)-4-[3-(4-chlorophenyl)-2-propynyloxy]-1,2,5-thiadiazole

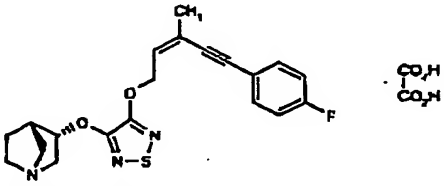


C17-H16-Cl-N3-O2-S; Mol wt: 361.85

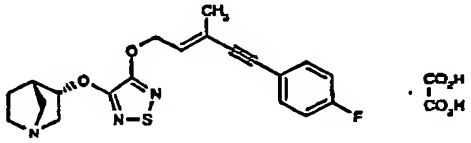
ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
258610	Me	OMe	H	$C_{18}H_{21}N_3O_7S.C_2H_2O_4$
258611	H	H	Cl	$C_{17}H_{16}ClN_3O_2S.C_2H_2O_4$
258612	Et	OMe	H	$C_{20}H_{23}N_3O_7S.C_2H_2O_4$
258613	i-Pr	OMe	H	$C_{21}H_{25}N_3O_7S.C_2H_2O_4$
258614	H	CF3	H	$C_{18}H_{16}F_3N_3O_2S.C_2H_2O_4$
258649	H	H	F	$C_{17}H_{15}FN_3O_2S.C_2H_2O_4$
259764	H	F	H	$C_{17}H_{14}FN_3O_2S.C_2H_2O_4$



258615: C20-H20-F-N3-O2-S.C2-H2-O4



259763: C20-H20-F-N3-O2-S.C2-H2-O4

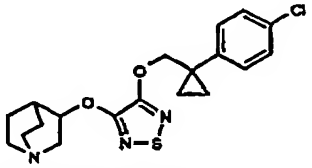
SOURCE – Lilly.

REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9740043.

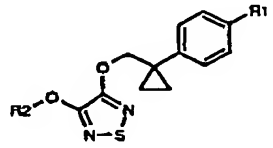
257733

(±)-3-[1-(4-Chlorophenyl)cyclopropylmethoxy]-4-(3-quinuclidinyloxy)-1,2,5-thiadiazole



C19-H22-Cl-N3-O2-S; Mol wt: 391.91

ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	Formula
258633	F	endo-(5R,6R)- -1-azabicyclo[3.2.1]oct-6-yl	$C_{19}H_{22}FN_3O_2S$
258636	Cl	2-azabicyclo[2.2.1]hept-6-yl	$C_{18}H_{20}ClN_3O_2S$
258637	Cl	3(R)-Pip	$C_{17}H_{20}ClN_3O_2S$

SOURCE – Lilly.

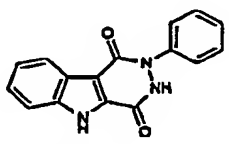
REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9740044.

TREATMENT OF CEREBROVASCULAR DISEASES

257448

2-Phenyl-2,3,4,5-tetrahydro-1*H*-pyridazino[4,5-*b*]indole-1,4-dione



C16-H11-N3-O2; Mol wt: 277.28

ACTION – Selective and noncompetitive NMDA receptor antagonist that preferentially binds to the strychnine-insensitive glycine binding site associated with the NMDA receptor complex. Compound blocked the response to NMDA in rat cortex slices (K_b < 150 µM) and displaced [^{3}H]-L-689560 binding to the strychnine-insensitive site in rat forebrain membranes (IC_{50} < 50 µM). Potentially useful in the treatment or prevention of neurodegenerative disorders such as stroke, cerebral ischemia, epilepsy, Huntington's chorea, Alzheimer's disease, Parkinson's disease and anoxia.

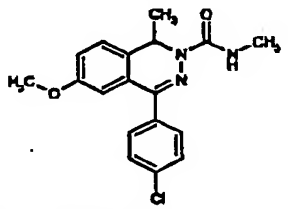
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Laddowahoty, T. and MacLeod, A.M. (Merck Sharp & Dohme, Ltd.) *Pyridazino-indole derivs.* US 5693640.

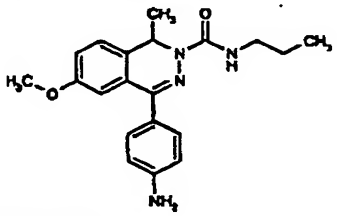
257717

4-(4-Chlorophenyl)-6-methoxy-*N*,1-dimethyl-1,2-dihydrophthalazine-2-carboxamide



C18-H18-Cl-N3-O2; Mol wt: 343.81

ACTION – A noncompetitive AMPA receptor antagonist potentially useful in the treatment of neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, hypoxia, anoxia, hypoglycemia, stroke, epilepsy, schizophrenia and migraine. Another specifically claimed compound from this series of phthalazine derivatives is:



258754: C20-H24-N4-O2

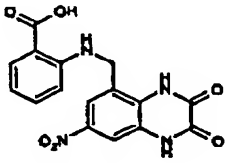
SOURCE – Schering AG.

REFERENCES

1. Ottow, E. et al. (Schering AG) *Phthalazine derivs., their preparation and their use as drugs.* DE 19617863, WO 9740020.

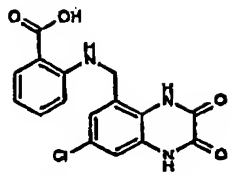
258857

2-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethylamino)benzoic acid



C16-H12-N4-O6; Mol wt: 356.29

ACTION – Dual glycine-site NMDA and AMPA receptor antagonist with respective IC_{50} values in binding assays of 0.05 ± 0.02 and 0.05 ± 0.01 µM. Potentially useful as a neuroprotective agent or for the treatment of epilepsy. Another compound from this series of 5-arylaminomethylquinoxaline-2,3-diones with selectivity for the glycine binding site of the NMDA receptor is:



258858: C16-H12-Cl-N3-O4

SOURCE – Novartis.

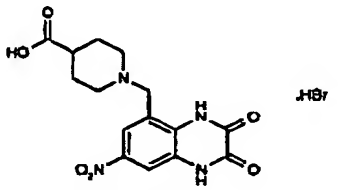
REFERENCES

1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalinyl derivs.* WO 9708155.

3. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part II: N-Aryl derivatives as novel NMDA/glycine and AMPA antagonists.* Bioorg Med Chem Lett 1998, 8(1): 71.

258859

1-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)piperidine-4-carboxylic acid hydrobromide



C15-H16-N4-O6.HBr; Mol wt: 429.23

ACTION – Potent and selective AMPA receptor antagonist, as shown in binding assays (IC_{50} = 0.07 µM), with good water solubility. It exhibited significantly weaker activity at the glycine binding site of the NMDA receptor (IC_{50} = 3.9 µM). Compound provided protection against electroshock-induced convulsions in mice with moderate potency (ED_{50} = 44 mg/kg i.p.), but ataxia was observed at doses near the ED_{50}.

SOURCE – Novartis.

REFERENCES

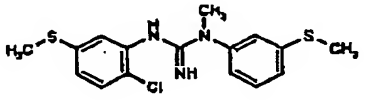
1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalinyl derivs.* WO 9708155.

2. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part I: A novel class of AMPA receptor antagonists.* Bioorg Med Chem Lett 1998, 8(1): 65.

CNS-5161

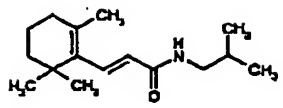
228550

*N*²-[2-Chloro-5-(methylsulfanyl)phenyl]-*N*¹-methyl-*N*¹-[3-(methylsulfanyl)phenyl]guanidine



C16-H18-Cl-N3-S2; Mol wt: 351.91

Hydrochloride salt, m.p. 203-4 °C.



266481: C16 H27 N O

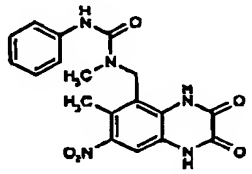
SOURCE – Shionogi.

REFERENCES

1. Kanemasa, T. et al. (Shionogi & Co. Ltd.) *P/Q Type calcium channel antagonist.* WO 9801121.

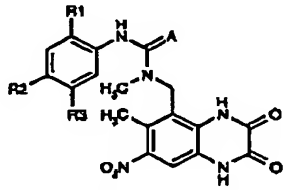
266182

N-Methyl-*N*-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)-*N'*-phenylurea



C18 H17 N5 O5; Mol wt: 383.3823

ACTION – Glutamate receptor antagonist acting at AMPA, kainate and, particularly, the glycine binding site of NMDA receptors (IC_{50} = 0.13, 0.82 and 0.008 µM, respectively). Claimed for the treatment of stroke, cerebral hypoxia/ischemia, Alzheimer's disease, Parkinson's disease and Huntington's disease. Within this series of substituted quinoxaline-2,3-diones, the following are also included:



Compound	R1	R2	R3	A	Formula
266915	H	OMe	H	O	$C_{19}H_{19}N_5O_6$
266916	H	OMe	H	S	$C_{19}H_{19}N_5O_5S$
266917	Me	Me	H	O	$C_{20}H_{21}N_5O_5$
266918	OMe	H	OMe	O	$C_{20}H_{21}N_5O_7$
266919	CF3	H	H	O	$C_{19}H_{16}F_3N_5O_5$
266920	H	CO2Et	H	O	$C_{21}H_{21}N_5O_7$

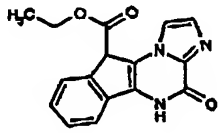
SOURCE – Warner-Lambert.

REFERENCES

1. Nikam, H.S. (Warner-Lambert Co.) *Urea and thiourea derivs. of substd. quinoxaline 2,3-diones as glutamate receptor antagonists.* WO 9823599.

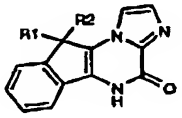
268738

4-Oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]-pyrazine-10-carboxylic acid ethyl ester



C16 H13 N3 O3; Mol wt: 295.2967

ACTION – Cerebral antiischemic and neuroprotective agent, an AMPA receptor antagonist that also acts as a noncompetitive glycine-site NMDA receptor antagonist. Within this series of specifically claimed imidazo[1,2-*a*]-indeno[1,2-*e*]pyrazin-4-one derivatives, the following are also included:



Compound	R1	R2	Formula
268738	CO2Et	H	$C_{16}H_{13}N_3O_3$
268739	1-Me-2-imidazolyl-CH2	H	$C_{18}H_{17}N_5O$
268740	(R)-HC(OMe)(Ph)CF3	H	$C_{22}H_{17}F_3N_4O_2$
268741	NH2	Me	$C_{17}H_{14}N_4O$
268742	-CH(3-NH2-Ph)-		$C_{23}H_{18}N_4O$
268743	CH2CH2CO2H	NH2	$C_{18}H_{18}N_4O_3$
268744	1-Me-5-imidazolyl-CH2	H	$C_{18}H_{17}N_5O$
268745	2-CO2H-1-pyrrolyl	H	$C_{20}H_{15}N_5O_3$
268746	NH2	Bu	$C_{17}H_{18}N_4O$

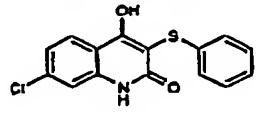
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Alaup, J.-C. et al. (Rhône-Poulenc Rorer SA) *Imidazo (1,2-a)-indeno (1,2-e) pyrazin-4-one derivs. and pharmaceutical compsns. containing same.* US 5807859, WO 9526350.

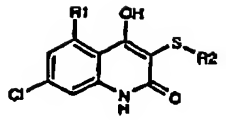
269005

7-Chloro-4-hydroxy-3-(phenylsulfanyl)quinolin-2(1*H*)-one



C15 H10 Cl N O2 S; Mol wt: 303.7680

ACTION – Potent and specific antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex, reported to possess good CNS penetration and high solubility. Claimed for the treatment or prevention of ischemic, hypoxic or hypoglycemic CNS damage, neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy and stroke, as well as for use as an anticonvulsant, analgesic, antidepressant, anxiolytic and antipsychotic agent. A representative compound from a series of quinolinic sulfide derivatives, wherein the following are also included: .



Compound	R1	R2	Formula
269006	H	3-Me-Ph	$C_{16}H_{12}ClNO_2S$
269007	H	3-Br-Ph	$C_{15}H_9BrClNO_2S$
269008	Cl	4-MeO-Ph	$C_{16}H_{11}Cl_2NO_3S$
269009	Cl	2-Br-Ph	$C_{15}H_8BrCl_2NO_2S$
269010	H	2-benzothiazolyl	$C_{18}H_9ClN_2O_2S_2$
269011	Cl	3-CO2H-2-Pyr	$C_{15}H_6Cl_2N_2O_4S$
269012	Cl	1,2,4-triazol-3-yl	$C_{11}H_6Cl_2N_4O_2S$
269013	H	4-(PhCH2CONH)-Ph	$C_{23}H_{17}ClN_2O_3S$
269014	Cl	4-(3-Pyr-CONH)-Ph	$C_{21}H_{13}Cl_2N_3O_3S$
269015	Cl	4-(4-Cl-PhCH2NH)-Ph	$C_{22}H_{16}Cl_2N_2O_2S$

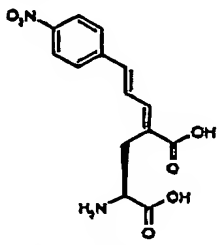
SOURCE – Korea Res. Inst. Chem. Technol., Taejon (KR).

REFERENCES

1. Park, K.S. et al. (Korea Res. Inst. Chem. Technol.) *Quinolinic sulfide derivs. acting as NMDA receptor antagonists and process for preparation thereof*, EP 869122, JP 98310575.

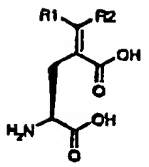
269083

(2*S*,*E*,*E*)-2-Amino-4-(4-nitrocinnamylidene)glutaric acid



C14 H14 N2 O6; Mol wt: 306.2726

ACTION – Neuroprotective agent, an ionotropic glutamate receptor agonist with selectivity for the GluR5 subtype (K_i < 1000 μM). Potentially useful for the treatment of neurodegenerative disorders such as stroke, cerebral ischemia, head and spinal cord trauma, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS-related dementia and Huntington's chorea, and also as an antipsychotic, anticonvulsant, analgesic, antiemetic, anxiolytic and antidepressant. Other specifically claimed glutamic acid derivatives include the following:



Compound	R1	R2	Formula
269084	4-N(Me)2-PhCH=CH	H	$C_{16}H_{20}N_2O_4$
269085	CH=CHPh	H	$C_{14}H_{13}NO_4$
269086	Bu	H	$C_{10}H_{17}NO_4$
269087	Me	Me	$C_8H_{13}NO_4$
269088	-(CH2)3-		$C_9H_{13}NO_4$
269089	4-Cl-Ph	H	$C_{12}H_{12}ClNO_4$
269090	-(CH2)5-		$C_{11}H_{17}NO_4$
269091	cyclopentyl	H	$C_{11}H_{17}NO_4$
269092	-(CH2)4-		$C_{10}H_{15}NO_4$

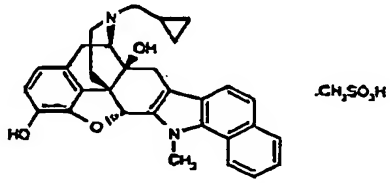
SOURCE – Lilly.

REFERENCES

1. Pedregal Tercero, C. and Rubio Esteban, A. (Lilly SA) *Glutamic acid derivs. and pharmaceutical compsns. for the treatment of central nervous system disorders*, EP 867430, JP 98279542.

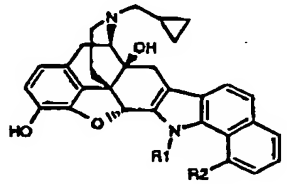
269145

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxy-1'-methyl-6,7-didehydro-1'*H*-benzo[6',7']indolo-[2',3':6,7]morphinan methanesulfonate



C31 H30 N2 O3 . C H4 O3 S; Mol wt: 574.6946

ACTION – Neuroprotective and cerebral antiischemic agent shown to exhibit potent protective effects against glutamate toxicity in cultured rat neurons (ED_{50} = 0.026 μM). It also reduced infarct volume in a rat model of middle cerebral artery occlusion–reperfusion injury (85% at 3 mg/kg i.p.). Other representative compounds within this series of indolomorphinane derivatives include the following:



Compound	R1	R2	X	Formula
269146	H	H	HCl	$C_{30}H_{29}N_2O_3HCl$
269147	H	Cl	MeSO3H	$C_{30}H_{27}ClN_2O_3CH_4O_3S$
269148	CH2Ph	H	MeSO3H	$C_{37}H_{34}N_2O_3CH_4O_3S$

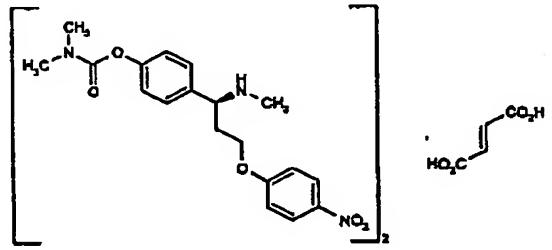
4. *Axonyx updates phenserine development progress.* DailyDrugNews.com (Daily Essentials) 2001, Sept 6.

5. *Novel memory-enhancing technology licensed by Axonyx from TJU.* DailyDrugNews.com (Daily Essentials) 2001, April 23.

RS-1259

316972

N,N-Dimethylcarbamic acid 4-[1(*S*)-(methylamino)-3-(4-nitrophenoxy)propyl]phenyl ester hemifumarate



2 C19 H23 N3 O5 . C4 H4 O4; Mol wt: 862.8850

ACTION – Orally active dual inhibitor of acetylcholinesterase (AChE) and 5-HT uptake with the ability to improve memory deficits in the place discrimination task in 24-month-old rats. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Sankyo.

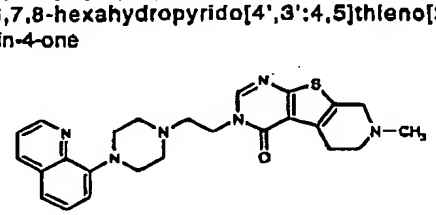
REFERENCES

1. Kaneko, T. et al. *RS-1259, an orally active dual inhibitor of AChE and 5-HT uptake as a potential therapy for Alzheimer disease.* Jpn J Pharmacol 2002, 88(Suppl. 1): Abst P-139.

TREATMENT OF CEREBROVASCULAR DISEASES

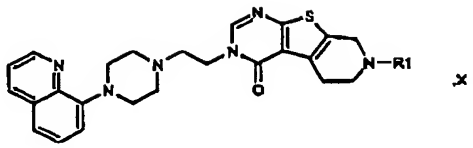
315353

7-Methyl-3-[2-[4-(8-quinolinyl)piperazin-1-yl]ethyl]-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]-pyrimidin-4-one



C25 H28 N6 O S; Mol wt: 460.6032

ACTION – Agent with affinity for 5-HT_{1A} receptors (K_i = 0.15 nM), potentially useful for the treatment of cerebral ischemia, as well as neurodegenerative diseases and brain trauma. Other exemplified substituted thienopyrimidine derivatives are:



Compound	R1	X	Formula
315354	H		$C_{24}H_{28}N_4OS$
315355	Et	2HCl	$C_{26}H_{32}N_4OS.2HCl$

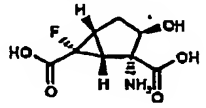
SOURCE – Abbott.

REFERENCES

1. Steiner, G. et al. (Knoll AG) *Substd. thienopyrimidine derivs. and the use thereof for the prophylaxis and therapy of cerebral ischaemia.* DE 10031389, WO 0202569.

315422

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-6-fluoro-3-hydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic acid



C8 H10 F N O5; Mol wt: 219.1670

ACTION – A representative compound from a series of bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives that acts as an agonist at group II metabotropic glutamate receptors. It was shown to inhibit forskolin-stimulated accumulation of cAMP in CHO cells with an IC_{50} of 476 nM. Potentially useful for the treatment of psychiatric and neurological disorders such as schizophrenia, anxiety, depression, bipolar disorder, drug abuse, Alzheimer's disease, Huntington's chorea, Parkinson's disease, muscular rigidity, cerebral ischemia, and head and spinal cord trauma.

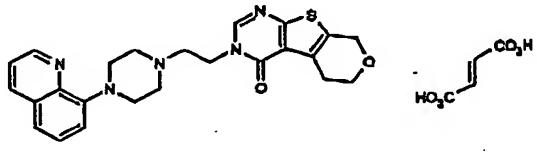
SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Novel dicarboxylic acid derivs.* WO 0200605.

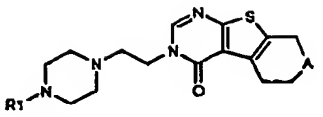
315726

3-[2-[4-(8-Quinolinyl)piperazin-1-yl]ethyl]-4,5,6,8-tetrahydro-3*H*-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one fumarate

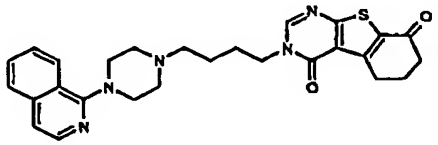


C24 H25 N5 O2 S . C4 H4 O4; Mol wt: 563.6321

ACTION – Agent with high affinity for 5-HT_{1A} receptors (K_i = 0.16 nM against receptors expressed in HEK293 cells), potentially useful for the treatment of neurodegenerative diseases, brain trauma and cerebral ischemia. Other exemplified pyrimidine derivatives include the following:



Compound	R1	A	Formula
315731	1-isoquinolyl	-O-	$C_{26}H_{25}N_5O_2S$
315732	1-isoquinolyl	-S(O)-	$C_{26}H_{25}N_5O_2S_2$
315733	1-isoquinolyl	-N(SO2Me)-	$C_{27}H_{28}N_6O_3S_2$
315739	8-quinolyl	-S-	$C_{26}H_{25}N_5OS_2$
315738	8-quinolyl	-S(O)-	$C_{26}H_{25}N_5O_2S_2$
315740	8-quinolyl	-N(SO2Me)-	$C_{27}H_{28}N_6O_3S_2$



315730: C27 H29 N5 O2 S

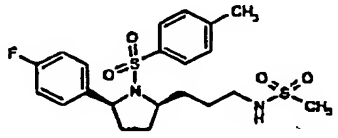
SOURCE – Abbott.

REFERENCES

1. Steiner, G. et al. (Knoll AG) *Pyrimidine derivs. and their use for preventing and treating cerebral ischaemia.* DE 10031390, WO 0202568.

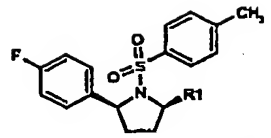
315763

N-[3-[(2*R**,5*R**)-5-(4-Fluorophenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-2-yl]propyl]methanesulfonamide

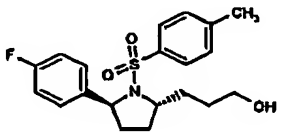


C21 H27 F N2 O4 S2; Mol wt: 454.5843

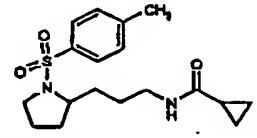
ACTION – A group I metabotropic glutamate receptor (mglu) agonist with an EC_{50} of 0.16 µM at rat $mglu_{1a}$ receptors expressed in EBNA cells. Potentially useful for the treatment of restricted brain function associated with bypass operations or poor blood supply, spinal cord and head trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, pain, schizophrenia, parkinsonism and conditions which lead to glutamate deficiency functions such as muscle spasms, convulsions, migraine, urinary incontinence, nicotine and opiate addiction, psychosis, anxiety, vomiting, dyskinesia and depression. Other exemplified sulfonylpyrrolidine derivatives are:



Compound	R1	Isomer	Formula
315764	CN	2R*,5S*	$C_{18}H_{17}FN_2O_2S$
315766	CH2Cl	2R*,5S*	$C_{18}H_{18}ClFNO_2S$
315769	cyclopropyl-CONHCH2	2R*,5S*	$C_{23}H_{25}FN_2O_3S$
315770	5-Me-1,2,4-oxadiazol-3-yl-CH2	2R*,5S*	$C_{21}H_{22}FN_3O_3S$
315776	2-Me-5-tetrazolyl-CH2	2R*,5S*	$C_{20}H_{22}FN_5O_2S$
315779	2-tetrazolyl-CH2CH2	2R*,5S*	$C_{20}H_{22}FN_5O_2S$
315780	1-imidazolyl-(CH2)3	2S,5S	$C_{23}H_{24}FN_3O_2S$
315781	4,6-(Me)2-2-pyrimidinyl-(CH2)3	2R*,5R*	$C_{26}H_{29}FN_4O_2S$
315782	1,3,4-oxadiazol-2-yl	2R*,5S*	$C_{19}H_{18}FN_3O_3S$
315783	2-tetrazolyl-(CH2)4	2R*,5R*	$C_{22}H_{26}FN_5O_2S$



315777: C20 H24 F N O3 S



315778: C18 H26 N2 O3 S

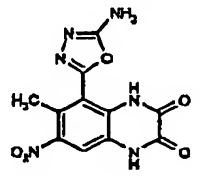
SOURCE – Roche.

REFERENCES

1. Mutel, V. and Wichmann, J. (F. Hoffmann-La Roche AG) *Sulfonyl-pyrrolidine derivs. useful for the treatment of neurological disorders.* WO 0202554.

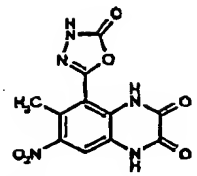
315794

5-(5-Amino-1,3,4-oxadiazol-2-yl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoxaline-2,3-dione



C11 H8 N6 O5; Mol wt: 304.2212

ACTION – Glutamate antagonist with *in vitro* activity against AMPA receptors and the glycine site of NMDA receptors. Potentially useful for the treatment of cerebral ischemia, chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and Huntington's disease, seizure disorders, schizophrenia, anxiety, pain and drug abuse. Another exemplified quinoxaline-2,3-dione derivative is:



315795: C11 H7 N5 O6

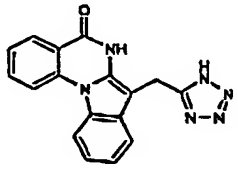
SOURCE – Pfizer.

REFERENCES

1. Kamboj, R.K. et al. (Pfizer Inc.) *Conformationally semi-constrained quinazoline 2,3-diones as neuroprotective agents.* US 6340758.

316105

7-(1*H*-Tetrazol-5-ylmethyl)indolo[1,2-*a*]quinazolin-5(6*H*)-one



C17 H11 N6 O; Mol wt: 316.3228

ACTION – A specifically claimed compound from a group of indolo[1,2-*a*]quinazolin-5-one derivatives effective as a poly(ADP-ribose) polymerase (PARP, NAD$^+$ ADP-ribosyltransferase) inhibitors. Potentially useful for the treatment of a broad range of conditions including apoptosis, neural tissue damage resulting from ischemia–reperfusion injury, neurological and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc., vascular stroke, cardiovascular disorders including myocardial infarction and unstable angina, age-related macular degeneration, AIDS, arthritis, atherosclerosis, cachexia, cancer, diabetes, head and spinal cord trauma, immune senescence, inflammatory bowel disorders, osteoporosis, pain, renal failure, retinal ischemia, septic shock and skin aging.

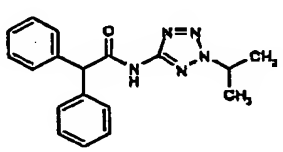
SOURCE – Novartis.

REFERENCES

1. Zimmermann, K. et al. (Novartis AG;Novartis-Erfindungen Vmbh) *Indoloquinazolinones.* WO 0206284.

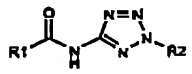
316188

N-(2-Isopropyl-2*H*-tetrazol-5-yl)-2,2-diphenylacetamide



C18 H19 N5 O; Mol wt: 321.3821

ACTION – Metabotropic glutamate receptor agonist giving an EC_{50} of 0.100 μM using rat $mglu_{1a}$ receptors expressed in EBNA cells. Potentially useful for the treatment of acute and chronic neurological disorders such as restricted brain function caused by bypass operations or transplant, poor blood supply to the brain, head and spinal cord trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, schizophrenia and idiopathic or medicament-related parkinsonism. Other exemplified tetrazole derivatives are:



Compound	R1	R2	Formula
316189	CH(Ph)2	Me	$C_{16}H_{15}N_5O$
316192	9H-xanthen-9-yl	Me	$C_{16}H_{13}N_5O_2$
316196	9H-xanthen-9-yl	i-Pr	$C_{18}H_{17}N_5O_2$
316197	CH(Ph)2	CH2CF3	$C_{17}H_{14}F_3N_5O$
316198	9H-xanthen-9-yl	CH2CF3	$C_{17}H_{12}F_3N_5O_2$
316199	6,11-dihydrodibenzo[b,e]oxepin-11-yl	Et	$C_{18}H_{17}N_5O_2$
316200	9-thioxanthenyl	Et	$C_{17}H_{15}N_5OS$
316202	2-MeO-9-xanthenyl	Et	$C_{18}H_{17}N_5O_3$

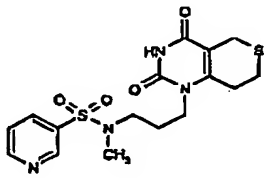
SOURCE – Roche.

REFERENCES

1. Jolidon, S. et al. (F. Hoffmann-La Roche AG) *Tetrazole deriva.* WO 0206254.

316201

N-[3-(2,4-Dioxo-2,3,4,5,7,8-hexahydro-1*H*-thiopyrano-[4,3-*d*]pyrimidin-1-yl)propyl]-*N*-methylpyridine-3-sulfonamide



C16 H20 N4 O4 S2; Mol wt: 396.4900

ACTION – A poly(ADP-ribose)polymerase (PARP, NAD$^+$ ADP-ribosyltransferase) inhibitor that displayed an IC_{50} of 0.04 μM against PARP, and was shown to protect endothelial cells from H_2O_2-induced toxicity with an IC_{50} of 0.25 μM. Potentially useful for the treatment of ischemia–reperfusion injury. Other exemplified uracil derivatives are: